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American Journal of Epidemiology
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Vol 133 No 11
Printed in U S A

Risk Factors for Respiratory Syncytial Virus-associated Lower Respiratory Illnesses in the First Year of Life

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The relation of breast feeding and other factors to the incidence of respiratory syncytial virus-associated lower respiratory tract illness (RSV-LRI) in the first year of life is examined. The study population is 1,179 healthy infants enrolled at birth between May 1980 and January 1984 into the Tucson Children's Respiratory Study, Tucson, Arizona. Each subject's data were assessed at each month of age during the first year of life, during those months when respiratory syncytial virus was isolated. A number of significant relations were observed, particularly between 1 and 3 months of age. At this age, the risk of having a RSV-LRI increased in association with <1-month or no breast feeding, with being male, and with increasing numbers of others sharing the child's bedroom. In multivariate analysis, only sex and the number of others sharing the room remained as significant direct effects. However, a significant interaction demonstrated that breast feeding has a protective role in relation to RSV-LRIs for those infants of mothers with a lower education level. The risk of having a RSV-LRI increases with combinations of risk factors. Being in day care was a significant risk factor in the 7- to 9-month age range. The RSV-LRI rate also varies by birth month. A separate case-control study assessed relations of RSV-LRIs with cord serum RSV antibody. Those with lower cord serum RSV antibody, who also have minimal breast feeding, were found to be especially at risk for RSV-LRIs in the first 5 months of life. *Am J Epidemiol* 1991;133:1135-51.

breast feeding; bronchiolitis; respiratory syncytial viruses; respiratory tract infections; risk factors

Respiratory syncytial virus (RSV) is a major cause of serious life-threatening illness of the lower respiratory tract in infancy (1). It is responsible for yearly epidemics, of approximately 5-month duration, which are closely associated with an increase in the numbers of infants and young children hospitalized with lower respiratory tract illnesses (LRI) (2).

While a variety of risk factors have been

Received for publication July 30, 1990, and in final form December 26, 1990.

Abbreviations: CI, confidence interval; LRI, lower respiratory tract illness; OR, odds ratio; RR, relative risk (ratio); RSV, respiratory syncytial virus; RSV-LRI, respiratory syncytial virus-associated lower respiratory tract illness.

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Supported by SCOR grant HL 14136 from the National Heart, Lung, and Blood Insitute.

The authors thank L. L. Minnich and B. W. Saul for their contributions to the analysis; B. A. Albright for secretarial assistance; and Dr. A. E. Camilli, Dr. M. Halonen, Dr. W. J. Morgan, and Dr. D. L. Shermil for help in the preparation of the manuscript.

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shown to be related to RSV infection (3, 4), these factors have not always been examined concurrently or on a monthly basis. Risk factors studied include sex, ethnicity, number of siblings and crowding, socioeconomic status, birth weight, maternal smoking, seasonality and birth month, and other social and family factors.

A protective effect of breast feeding against hospitalization due to RSV infection has been demonstrated by some studies (5). However, this effect has not always been statistically significant when controlling simultaneously for a number of confounders (4). No significant differences were found, in a nonhospitalized population, in the rates or distributions of infection with RSV in relation to feeding practices (6); however, trends toward decreased morbidity in the breast-fed group were present, especially in the early months of life. These effects have also been shown to vary with infant age and the amount and exclusivity of breast feeding (7–10).

A number of studies have shown an inverse relation between severity of RSV infection and levels of antibody in sera collected near the time of onset of illness (3, 11). Additionally, higher antibody titers at birth are associated with an older age at the time of infection (3) and lower rates of RSV infection in the first 6 months of life (12). Some studies, such as that by Toms et al. (13), suggest that maternal antibodies may act indirectly by protecting the mother and, hence, reducing the risk of viral transmission to the infant in the first month of life; others would suggest a more direct role for maternal antibody (14). Also, human colostrum has been shown to contain neutralizing activity against RSV in vitro (5, 15). Conversely, results of trials of inactivated RSV vaccine in infants have led to the suggestion that antibodies against some components of RSV may be involved in the pathogenesis of severe bronchiolitis (12, 16). However, the relations of breast feeding or breast milk and cord serum antibody titer to RSV infections have not been examined concurrently in a community population of infants.

We have examined many of these factors in the Tucson Children's Respiratory Study. The Children's Respiratory Study is a prospective study of respiratory illness in childhood, investigating the risk factors for and sequelae of acute LRIs in a large cohort of infants followed from birth (17, 18). The aim of the present investigation is to examine, prospectively, in this predominantly outpatient population of infants the possible interrelations of breast feeding, RSV antibody at birth, and other factors (sex, ethnicity, maternal education, the number of others sharing the child's room, maternal smoking, and day care) to the incidence of respiratory syncytial virus-associated lower respiratory tract illnesses (RSV-LRIs) in the first year of life.

Two approaches are used in our analyses: 1) In the total population, relations are assessed between RSV-LRIs and all risk factors considered, except cord serum RSV antibody level; and 2) questions relating to cord serum RSV antibody level are addressed in a subpopulation using a case-control study design.

MATERIALS AND METHODS

Total population study

The study population consists of 1,179 healthy infants, enrolled at birth into the Tucson Children's Respiratory Study between May 1980 and January 1984, and includes illnesses observed until December 1985. Eligible participants were those who planned to use the pediatricians of the largest local health maintenance organization in Tucson. This number (1,179) represents those who were followed by the health maintenance organization pediatricians during all or part of their first year of life. Children were given a follow-up time of 12 months if parents stated they still used the health maintenance organization pediatricians on a follow-up questionnaire completed in the child's second year of life (1.6 ± 0.35 (mean ± standard deviation) years), or if the child was seen for a "well-baby" visit between 12 and 15 months. Other children are assigned a follow-up time based on their age at their last recorded well-baby visit.

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All LRIs were diagnosed by the pediatricians, at the time of the office visits for the illnesses, according to criteria agreed upon by the pediatricians and the investigators (17). Nasopharyngeal and throat specimens were collected at the time of the LRI for viral cultures and for examination by immunofluorescent techniques to detect the presence of RSV and other viruses (18). An episode was considered to be RSV positive if either culture, immunofluorescence, or both were positive.

Information concerning duration of breast feeding in the first year of life was derived from a combination of data from two sources: prospectively from well-baby visits and retrospectively from questionnaires completed by parents when enrollees were in the second year of life (19, 20). There was excellent concordance (90 percent) between the two sources. Priority was given to the prospective data that were used for 72 percent (705/982) of those with information from either source. There were 197 (16.7 percent) infants with insufficient or no information from either source. Duration of breast feeding from both sources was grouped into the following categories: none, <1 month, 1–3 months, 4–6 months, and >6 months.

Exclusive breast feeding was distinguished from breast feeding in combination with milk and/or formula using the following categories derived from questions asked prospectively at the 2-month well-baby visit: breast feeding only at 2 months, breast feeding plus formula at 2 months, and no breast feeding at 2 months (milk or formula only). Similar variables were derived from information collected at the 4-, 6-, 9-, and 12-month well-baby visits. Information on other factors considered in this analysis came from questionnaires completed by the parents at enrollment: maternal education (≤12 years, >12 and ≤16 years, and >16 years); the number of persons sharing the same bedroom as the child (none, one, and two or more persons); birth month (December to February, March to May, June to August, and September to November); sex; maternal ethnicity (Anglo and others); and maternal smoking. Information obtained in the second year of life questionnaire as to whether or not a child spent ≥9 hours per week in day care was also considered.

Statistical analysis. The percentage of RSV-positive LRIs with respect to all LRIs studied virologically was calculated for each month during the entire study period (from May 1980 to December 1985). Data from those months during the study period when RSV was isolated were used for subsequent analysis. Since RSV occurs in epidemics, these were the months when infants were considered at risk for RSV-LRIs. During these months, the appropriate status was assigned to each subject for each month of age in the first year of life, within a subject's follow-up period, e.g., RSV-positive LRI, RSV-negative LRI, no RSV virologic study done, or no LRI. Only the first RSV-LRI episode was considered, and subjects were excluded from analyses in subsequent months following a RSV-LRI. For calculating incidence measures, RSV-negative LRIs and those for which no virologic data were obtained were ultimately combined with cases with no LRI. If any of these cases are misclassified, the resulting bias would be toward the null hypothesis of no effect. There were 31 LRIs with no virologic information, including three in the 1- to <3-month age range; removing these from analyses did not affect the results. In addition, 56 infants were excluded as their follow-up times in the first year of life did not include a RSV season.

Two parameters were derived from the data. 1) Person-time incidence rates (21) expressed the rate of first RSV-associated LRIs per 1,000 person-months at risk, cumulated by month of age both overall and for factors of interest. The following equation calculates the person-time incidence rate at month m, where m is from 1 to 12 months.

$$\text{Rate at month } m = \frac{\text{no. of RSV-LRIs (0–}m\text{ months)}}{\text{no. of person-months (0–}m\text{ months)}} \times 1{,}000$$

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This measure gives an overall cumulated rate per 1,000 per month up to each month of age in the first year of life. Plots show this rate on the ordinate. 2) Incidence rates per 100 children at risk for RSV-LRIs were calculated for each month of age, both overall and for subcategories of the factors of interest, in order to evaluate effects by month of age in the first year of life.

These incidence measures may frequently be referred to as attack rates, since the population is at risk for RSV-LRIs only during the limited time period of the RSV epidemic (22).

The statistical significance of associations and trends between the various factors and the incidence by month of age was assessed bivariately using the χ^2 distribution with Yates' correction where appropriate. Relative risks (RRs) were computed as follows.

$$RR = \frac{\% \text{ with RSV-LRIs among those with risk factors}}{\% \text{ with RSV-LRIs among those without risk factors}}$$

Also calculated were 95 percent confidence intervals (CI). Kendall's tau (one-tailed) was used as a nonparametric measure of correlation or trend. Data were also evaluated in 2-month intervals, where rates were similar by month. Additionally, variables were combined to assess relative risks of a combination of risk factors. To assess multivariate effects, log-linear modeling was done using saturated models, and partial χ^2 statistics were computed to determine statistical significance of effects at an α-level of 0.05. The partial χ^2 is the difference between the goodness-of-fit test statistic (likelihood-ratio χ^2) with and without the term or effect being tested. It also has a χ^2 distribution (one-tailed) and can be used to test the hypothesis that the effect is zero (23). Adjusted odds ratios (OR) were derived from the model coefficients.

RSV antibody case-control study

The case-control study was limited to the larger group of infants of Anglo maternal ethnicity. RSV-positive LRIs were identified in 135 infants with follow-up times of 1 year: 94 of these were of Anglo maternal ethnicity. The latter were matched with Anglo infants for sex, and month of birth with infants who were also followed for the entire first year, but with no LRI. Cord sera were available on 86 matched pairs of Anglo infants who also had breast feeding information.

The level of RSV antibody in cord sera was determined as previously described (24). Initial 1:10 serum dilutions were prepared in phosphate-buffered saline with subsequent 1:20–1:640 serial dilutions. Sera were overlaid onto wells containing RSV-infected and -uninfected, acetone-fixed cells and incubated at 35–37°C for 30 minutes. Wells were washed twice for 5 minutes in phosphate-buffered saline and then overlaid with appropriately diluted fluorescein isothiocyanate-conjugated goat anti-human immunoglobulin G (heavy and light chain specific). They were incubated at 35–37°C for 30 minutes and subsequently washed twice in phosphate-buffered saline. Buffered glycerol was used as the mounting medium, and wells were examined with a Zeiss epifluorescence microscope for specific granular cytoplasmic fluorescence ≥1+ in intensity to determine the end-point dilution.

Statistical analysis. Odds ratios were calculated both for single factors and while controlling for other factors by stratification. Mantel-Haenszel estimates of adjusted odds ratios and 95 percent confidence intervals were calculated (25). Logistic regression was also performed to provide odds ratios while controlling for other risk factors.

All statistical analysis used SPSSX or SPSS-PC software and custom programs.

RESULTS

Total population study

Of a total of 460 LRIs in the first year of life, 12 (2.6 percent) required the infant to be hospitalized, and 375 (82 percent) had virologic studies. There were 148 (39.5 percent) episodes positive for RSV, including five repeat RSV infections that were excluded from analysis. Of the 143 remaining RSV-positive LRIs, 123 (86 percent) were

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diagnosed as bronchiolitis, and 121 (84.6 percent) were associated with wheezing on examination, the majority (94 percent) of which were bronchiolitis. Information from a nurse-administered parental questionnaire at a convalescent visit indicated that the duration of illnesses ranged from <1 week (7 percent) to >3 weeks (18 percent), with a maximum frequency of 32 percent of illnesses lasting 7–10 days. Two cases diagnosed as bronchiolitis were hospitalized. In addition, there were 67 other LRIs associated with wheezing but not with RSV. Of the 375 LRIs studied virologically, RSV was detected most often with 39.5 percent, followed by parainfluenza virus type 3 in 34 (9 percent) instances, none of which was a repeat infection; detection rates were 1–5 percent for the other viruses assayed (parainfluenza virus types 1 and 2, influenza virus types A and B, adenoviruses, enteroviruses, cytomegalovirus, and rhinovirus).

The monthly distribution of the percentage of positive RSV results among all LRIs studied virologically for children <1 year of age was similar for each study year. Study years were combined, therefore, and figure 1 shows the combined distribution by month for the study years 1980–1985. RSV is clearly epidemic in nature, occurring from October to April and peaking in January. This distribution compares well with that for positive RSV results among all LRIs (n = 1,052) diagnosed in the study until October 1986 (17).

Table 1 indicates the distribution of the study population by the various risk factor categories of interest considered in this analysis. Not all subjects had complete sets of information. There were a number of significant relations within this set of variables. Infants who were breast-fed the longest were more likely to have Anglo nonsmoking mothers with more education, to have fewer persons sharing the bedroom, and to be less likely in day care ($p < 0.005$, adjusted for multiple comparisons). Neither birth month nor sex was associated with any other risk factor considered in this analysis.

Incidence rate per 100 infants by month. The incidence of RSV-LRIs per 100 infants by month of age (figure 2) is fairly constant during the 3- to 7-month age range at 3.7–4.0 per 100 infants at risk each month, after which it decreases. No RSV-LRIs were observed before 1 month of age. Rates were similar in the 2-month intervals after 1 month of age, and subsequent analysis of incidence rates per 100 children combined data into 2-month intervals as follows: 1–<3 months, 3–<5 months, 5–<7 months, 7–<9 months, and a final interval of 9–<12 months. Two RSV-LRIs identified at 12 months are excluded.

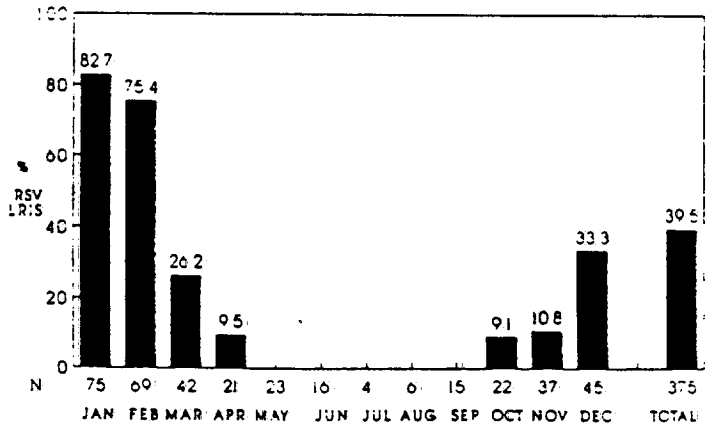

FIGURE 1. Positive respiratory syncytial virus results by percentage among all lower respiratory tract illnesses studied virologically by month in a health maintenance organization study population, Tucson, Arizona (1980–1985). RSV-LRI, respiratory syncytial virus-associated lower respiratory tract illness; N, number of cases.

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TABLE 1. Distribution of factors considered in a health maintenance organization study population, Tucson, Arizona, 1980–1985

Variable	No.	%
Duration of breast feeding		
None	157	13
<1 month	53	4
1–3 months	235	20
4–6 months	152	13
>6 months	385	33
Missing information	197	17
Exclusivity of breast feeding at 2 months		
Exclusively breast-fed	458	39
Breast + formula	236	20
No breast feeding	335	28
Missing information	150	13
Maternal education		
≤12 years	375	32
>12–≤16 years	593	50
>16 years	206	18
Missing information	5	<1
No. sharing same room		
None	689	58
One	299	25
Two or more	167	14
Missing information	24	2
Birth month		
January–March	198	17
April–June	289	24
July–September	366	31
October–December	326	28
Sex		
Male	575	49
Female	601	51
Missing information	3	<1
Ethnicity		
Anglo	874	74
Hispanic	221	19
Other	81	7
Missing information	3	<1
Maternal smoking		
Yes	204	17
No	972	82
Missing information	3	<1
Day care		
Yes	467	40
No	532	45
Missing information	180	15
Total	1,179	100

Table 2 shows univariate relations between the risk factors considered and the incidence of RSV-LRIs per 100 children between the ages of 1 and <3 months. (Relative risks are included as risk ratios with confidence intervals.) For breast-feeding status, RSV-LRI rates were similar in the categories of <1 month and no breast feeding (4.7 percent and 6.9 percent, respectively), which were combined into one category called "minimal" breast feeding. The relative risk of RSV-LRIs associated with minimal breast feeding at this age was 2.5. In addition, the relative risk increased from 2.2 for those who were breast-fed and also given formula to 4.0 for those given formula or milk only, when compared with those who were exclusively breast-fed at 2 months of age, with a statistically significant trend ($p = 0.01$). Similar trends of borderline significance were observed when considering RSV-LRIs at 1–<2 months and 2–<3 months of age.

No other significant protective effects of breast feeding were observed at any other age up through 12 months. (The RRs for having a RSV-LRI with minimal breast feeding for other age intervals were as follows: 3–<5 months, RR = 0.9; 5–<7 months, RR = 0.7; 7–<9 months, RR = 1.2; 9–<12 months, RR = 0.33.) Breast feeding at the time coincident with the month of age being analyzed also showed no additional protective effect.

Several factors other than breast feeding are also significantly related to the incidence of RSV-LRIs in the first year of life. Infants of mothers with a high school education or less had a higher incidence (5.3 percent) of RSV-LRIs between 1 and <3 months compared with 1.7 percent in the infants of mothers with more education (table 2). There was no significant difference in the incidence of RSV-LRIs when comparing infants of mothers with 12–16 years and >16 years of education. No significant trends associated with maternal education were observed beyond 3 months of age.

The incidence of RSV-LRIs per 100 children between 1 and <3 months was significantly higher in males (4.3 percent) compared with females (1.3 percent) (table 2). However, this effect was predominantly due to Hispanic males; 44 percent of 16 infants between 1 and <3 months of age with RSV-

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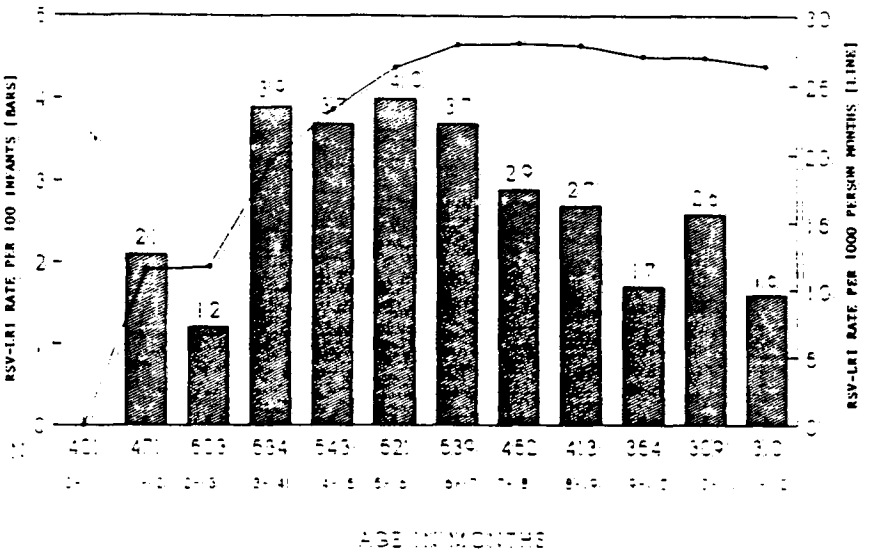

FIGURE 2. Rates of respiratory syncytial virus-associated lower respiratory tract illnesses in the first year of life, in a health maintenance organization study population, Tucson, Arizona (1980–1985). RSV-LRI, respiratory syncytial virus-associated lower respiratory tract illness; N, number of cases. (For rates above, see Materials and Methods for calculation.)

LRIs were Hispanic males; none was an Hispanic female. This also accounts for the significantly higher incidence of RSV-LRIs between 1 and <3 months of age among infants of Hispanic origin compared with Anglos (table 2). No consistent trends were observed beyond this age in the relation of RSV-LRIs to sex or ethnicity.

There was a significant increase in the RSV-LRI incidence in association with increasing numbers of others sharing the same bedroom with the child from 1–5 months of age, with trends of borderline significance from 6 to 12 months. Table 2 shows a significant trend for rates between 1 and <3 months of age, with a relative risk of 1.6 for one person sharing and 4.7 for two or more persons sharing compared with none sharing. At 3–<5 months, the equivalent relative risks are 3.9 and 6.1, again with a significant trend ($p < 0.002$).

Between 7 and <9 months of age, those in day care had an incidence rate of RSV-LRIs of 6.7 per 100 children versus 2.4 for those not in day care ($\chi^2 = 4.4$, $p = 0.04$). Between 9 and <12 months, the same trends were seen, but they were of borderline statistical significance. No significant trends relating day care to RSV-LRIs were seen below 7 months of age.

Maternal smoking was not related to the incidence of RSV-LRIs at any age in the first year of life.

Incidence rate per 1,000 person-months. The cumulated rate of RSV-LRIs per 1,000 person-months, from 1–12 months of age, is superimposed on figure 2. This rate is low in the first few months (12/1,000 person-months), increases until 6 months of age (26/1,000 person-months), and then levels off. This cumulated measure acts as a smoothing function in that it reduces the amount of variation or fluctuations present in the data by month. Although the incidence per 100 children is fairly constant between 3 and 7 months, the person-time incidence rate (per 1,000 person-months) increases until 7 months, since it is constrained by the low initial rate, and increases as successive RSV-LRI occurrences and person-months are added. After 6–7 months, the cumulated measure levels off as the incidence per 100 children by month decreases. The person-time incidence rate of RSV-LRIs for the entire first year of life is 26.4 per 1,000 infants per month.

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TABLE 2. Single-factor relations with RSV-LRIs† between 1 and <3 months of age, in a health maintenance organization study population, Tucson, Arizona, 1980–1985

Variable	No.	RSV-LRIs (%)	RR†	*p* value (Kendall's tau)
Breast feeding				
None–<1 month	114	5.3	2.5 (0.9–7.0)‡	0.04
1 month or more	380	2.1		
Amount of breast feeding at 2 months				
Formula and/or milk	177	5.1*	4.0 (1.1–14.1)	0.01
Breast + formula	105	2.9	2.2 (0.5–10.9)	NS†
Exclusively breast-fed	234	1.3		
Maternal education				
≤12 years	170	5.3	3.1 (1.2–8.2)	0.01
>12 years	409	1.7		
Sex				
Male	280	4.3	3.2 (1.0–9.8)	0.02
Female	297	1.3		
Ethnicity				
Hispanic and other	148	4.7	2.3 (0.9–6.0)	0.05
Anglo	431	2.1		
No. sharing child's room				
Two or more	74	8.1**	4.7 (1.6–14.2)	0.001
One	147	2.7	1.6 (0.5–5.5)	NS
None	349	1.7		
Maternal smoking				
Yes	108	2.8	1.0 (0.3–3.5)	NS
No	471	2.8		

* Trend $p = 0.01$, ** trend $p = 0.007$.

† RSV-LRI, respiratory syncytial virus-associated lower respiratory tract illness; RR, relative risk (ratio) (percentage with RSV-LRIs among those with risk factor/percentage with RSV-LRIs among those without risk factor); NS, not significant.

‡ Numbers in parentheses, 95% confidence interval.

Figure 3 indicates the rates of RSV-LRIs per 1,000 person-months differentiated by the duration of breast feeding in three categories (minimal, 1–6 months, >6 months). Through 5 months of age, those who receive minimal breast feeding appear more likely to have RSV-LRIs than those who are breast-fed longer. After 5 months of age, there appears to be little or no protective effect. These trends are statistically significant using the χ^2 distribution ($p < 0.05$) at 1–<2 months only and of borderline significance between 1 and <3 months of age when considering minimal breast feeding versus other categories combined. The use of different category combinations (including none, <1-month, and 1- to 3-month breast feeding) confirmed that the significant difference was consistently between minimal and >1-month breast feeding in the 1- to <3-month age range, consistent with the analysis of the incidence per 100 infants by month of age.

Figure 4 illustrates how the incidence rate per 1,000 person-months (person-time incidence rate) varies by month of age according to birth month. The distribution of incidence rates is displaced along the *x*-axis, depending on when a child was born in relation to the RSV season. For those born in the first half of the RSV season (from October to December), the rate increases until 5 to 6 months of age, whereas the rate for those born in the latter half of the RSV season remains fairly constant until the next RSV season is encountered. The distributions of those born 1–3 and 3–6 months prior to the RSV season are displaced along the *x*-axis accordingly.

Considering the entire first year of life, the

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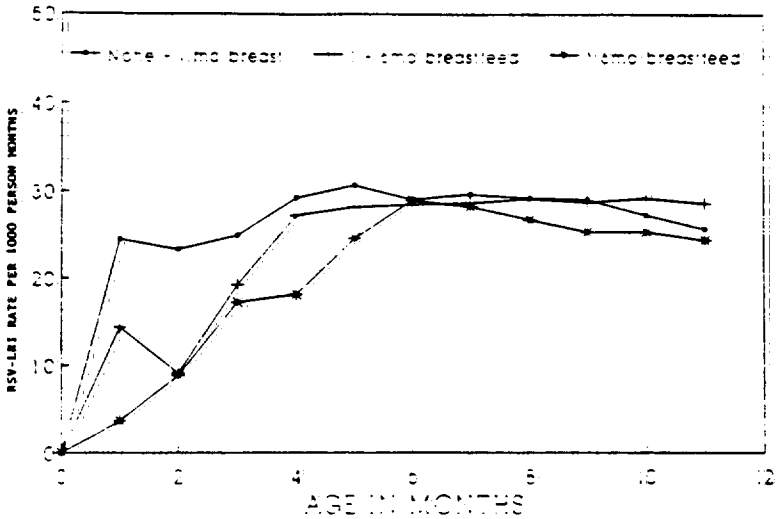

FIGURE 3. Person-time incidence rates of respiratory syncytial virus-associated lower respiratory tract illnesses up to 12 months of age by breast feeding, in a health maintenance organization study population, Tucson, Arizona (1980–1985). RSV-LRI, respiratory syncytial virus-associated lower respiratory tract illness. (See Materials and Methods for calculation of person-time incidence rates.)

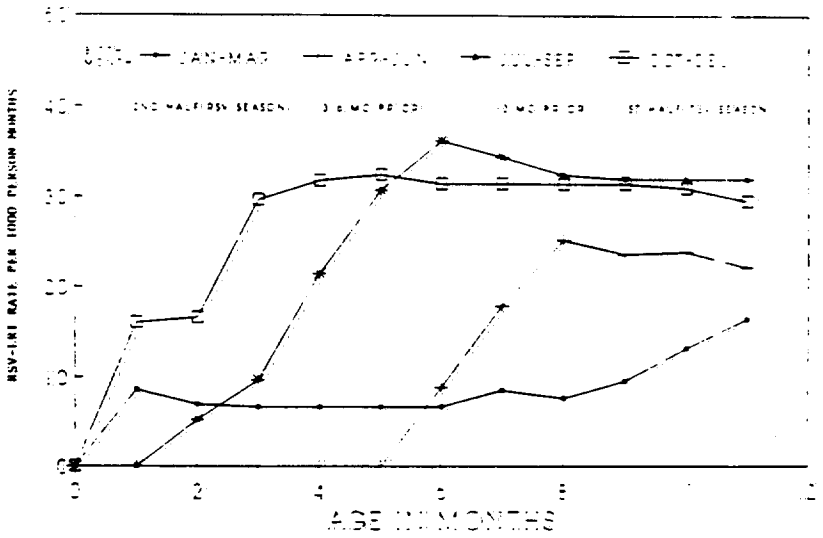

FIGURE 4. Person-time incidence rates of respiratory syncytial virus-associated lower respiratory tract illnesses up to 12 months of age by birth month in a health maintenance organization study population, Tucson, Arizona (1980–1985). RSV-LRI, respiratory syncytial virus-associated lower respiratory tract illness; mo, month. (See Materials and Methods for calculation of person-time incidence rates.)

incidence of RSV-LRIs was 16.7 for those born from July to September and 15.6 for those born from October to December, compared with 9.5 and 11.7 for birth months January–March and April–June, respectively. Combining these categories gives an incidence of 16.2 percent for those born from July to December, which is signifi-

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cantly different from the incidence of 10.8 percent for those born from January to June ($\chi^2 = 5.16$; $p < 0.02$).

Multivariate analysis. Variables considered for multivariate analysis were those that had shown some statistically significant association with the incidence of RSV-LRIs and an elevated relative risk during each 2-month age interval. Variables included were the following: duration (minimal versus >1 month) and exclusivity of breast feeding (breast only, breast plus formula, formula/milk only at 2 months); maternal education; number sharing the child's room; sex; and ethnicity. (Maternal smoking showed no significant contribution to multivariate analysis when investigated.) Day care was included in analyses after 7 months of age. All variables were collapsed into dichotomous categories (except the exclusive breast-feeding variable) as follows: maternal education, ≤12 years versus >12 years; none/one sharing the room versus two or more; Anglo versus Hispanic and other ethnicities. For each 2-month age interval, log-linear analysis was used to assess relations between RSV-LRIs and other risk factors.

At 1–<3 months of age, relations between RSV-LRIs, exclusivity of breast feeding, and other risk factors were evaluated. No direct effect remained for exclusivity of breast feeding after controlling for all other variables. However, there was a significant interaction between the incidence of RSV-LRIs, years of maternal education, and exclusivity of breast feeding (partial χ^2, $p < 0.01$), after accounting for all other effects. This interaction is shown in figure 5. It is apparent, although cell sizes are small, that in the lower maternal education category, there is a significant increasing trend in the incidence of RSV-LRIs between 1 and <3 months of age, from exclusively breast-fed infants (0.0 percent) to breast- and formula-fed infants (3.3 percent) to those fed formula or milk only (9.6 percent) (tau $p = 0.02$). The odds ratio for having a RSV-LRI in those infants of mothers with a low educational level who were not breast-fed was 6.8 (95 percent CI 0.8–56.0). This effect was seen with trends of borderline significance in Anglo males and females and in Hispanic males, although numbers are small; there are no RSV-LRIs in Hispanic females in this age range. There is no such association in the higher maternal education category. An equivalent analysis substituting duration for exclusivity of breast feeding gave similar results.

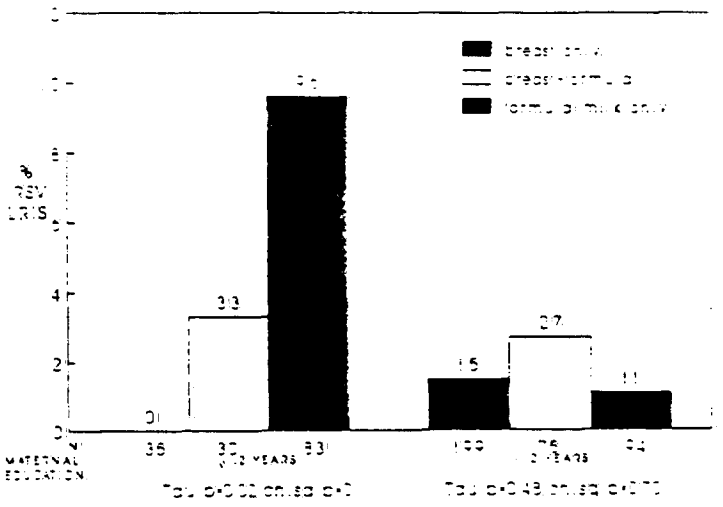

FIGURE 5. Incidence rates of respiratory syncytial virus-associated lower respiratory tract illnesses between 1 and <3 months of age by maternal education and breast-feeding status, in a health maintenance organization study population, Tucson, Arizona (1980–1985). RSV-LRI, respiratory syncytial virus-associated lower respiratory tract illness; N, number of cases.

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After accounting for all other interactions and effects at 1–<3 months of age, significant direct effects remained only for sex (partial χ^2, $p = 0.04$) (OR = 1.6; 95 percent CI 0.7–3.7) and for number sharing the child's room (partial χ^2, $p = 0.03$) (OR = 5.3; 95 percent CI 2.3–12.2). The bivariate relation seen between RSV-LRIs and ethnicity at this age was not significant after controlling for other effects, mainly because it is observed as an interaction among RSV-LRIs, sex, and ethnicity (partial χ^2, $p < 0.03$).

Table 3 shows different combinations of three risk factors (two or more sharing the child's room, low maternal education, and minimal breast feeding) assessed in relation to RSV-LRIs. The relative risk of having a RSV-LRI increases from 4.0 for those who had two or more persons sharing their room, to 5.6 for those who also have a low maternal education, to 8.0 when little or no breast feeding is included; all combinations are highly significant. Similar relations were observed in both males and females and for both ethnic groups, although the trends did not always reach statistical significance.

Log-linear analyses performed for other 2-month age intervals showed that direct effects persisted only for sharing the room with two or more people in the 3- to <5-month age range (OR = 3.7; 95 percent CI 1.6–8.7; partial χ^2, $p < 0.01$) and a smaller effect for day care in the 7- to <9-month age range (OR = 1.4; 95 percent CI 0.7–2.9; partial χ^2, $p < 0.03$), after controlling for other variables and effects.

RSV antibody case-control study

The cord serum RSV antibody titer in the 86 matched pairs ranged from <10 (undetectable) to 2,560. The distribution was positively skewed (3.6) with a median value of 80. A $\log_{10}$ transformation (assigning the value of 5 to undetectable titers) reduced the skew to 0.06, giving a geometric mean of 117 (standard deviation, 3.5). Because of its distribution, the cord serum RSV antibody titer was considered as a categorical variable, initially in four categories: 0–20, 40–80, 160–320, and ≥640. There was a distinct drop in the percentage of RSV-LRIs in the last two categories. Subsequently, two categories were used for analysis: 0–80 (low-titer group) and ≥160 (high-titer group), which

TABLE 3. Multivariable relations with RSV-LRIs* between 1 and <3 months of age, in a health maintenance organization study population, Tucson, Arizona, 1980–1985

Variable	No.	RSV-LRIs (%)	RR*	p value (Kendall's tau)
Two or more sharing room	74	8.1	4.0 (1.5–10.7)†	0.002
None or one sharing room	476	2.0		
Two or more sharing room and maternal education ≤12 years	43	11.6	5.6 (2.0–15.3)	0.0001
All other combinations of sharing and maternal education	527	2.1		
Two or more sharing room, maternal education ≤12 years, and minimal breast feeding	21	19.0	8.0 (2.8–22.8)	0.00001
All other combinations of sharing, maternal education, and feeding	505	2.4		

* RSV-LRI, respiratory syncytial virus-associated lower respiratory tract illness; RR, relative risk (ratio) (percentage with RSV-LRIs among those with risk factors/percentage with RSV-LRIs among those without risk factors).
† Numbers in parentheses, 95% confidence interval.

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divides the distribution approximately at the median.

In the first year of life, the percentage of RSV-LRIs in those with a low cord serum RSV antibody titer was 56.3 compared with 44 percent in the high-titer group, with an OR for having a RSV-LRI with lower cord serum RSV antibody levels of 1.67 (95 percent CI 0.9–3.1; χ^2, $p = 0.13$). Similar trends were seen in the 57 matched pairs <7 months of age (55 percent vs. 43 percent; OR = 1.66; 95 percent CI 0.8–3.5) and in the 22 matched pairs from 7 to 12 months of age (59 percent vs. 44 percent; OR = 1.81; 95 percent CI 0.6–5.3). Stratifying and adjusting for breast feeding gave a Mantel-Haenszel odds ratio of 1.6 (95 percent CI 0.9–3.0; χ^2, $p < 0.1$). Stratifying and adjusting for maternal education also gave an odds ratio for having a RSV-LRI with lower cord serum RSV antibody of 1.6 (95 percent CI 0.9–3.0; χ^2, $p < 0.1$) with no evidence of interaction.

However, a combination of three risk factor categories, i.e., lower cord serum RSV antibody, lower maternal education, and minimal breast feeding, gave an increased odds ratio of 4.4 (95 percent CI 1.1–18.3; χ^2, $p < 0.05$), compared with infants in the reference group who were breast-fed, had higher cord serum RSV antibody, and had higher maternal education. All other combinations of risk factor categories gave an odds ratio of 1.6 (95 percent CI 0.8–3.2; χ^2, $p < 0.25$), compared with the reference group.

Using logistic regression to assess the relation between RSV-LRIs and antibody level while controlling for maternal education and breast-feeding status gave an odds ratio for having a RSV-LRI with a low antibody level of 1.6 (95 percent CI 0.8–2.9; $p < 0.1$). Low maternal education was associated with an odds ratio for having a RSV-LRI of 2.5 (95 percent CI 1.2–5.2; $p < 0.01$). Breast feeding was not a significant contributor to this model, and no additional risk associated with an interaction between low cord serum RSV antibody and minimal breast feeding was demonstrated.

Since cases were matched with controls for birth month and sex, there was no relation between these factors and RSV-LRIs in this case-control subgroup. However, those born from January to June were more likely to have a higher cord serum RSV antibody titer (>80) than were those born from July to December (64 percent vs. 42 percent: χ^2, $p = 0.01$). There was no statistically significant relation between age at the time of the RSV-LRI and the level of cord serum RSV antibody.

Of the 86 matched pairs, 25 matches were in the age range of <5 months, which provided an adequate number to analyze, at least bivariately. In this younger age range, there was no association between RSV-LRIs and RSV antibody level (OR = 1.0; 95 percent CI 0.3–3.0; χ^2, $p = 1.0$). However, the odds ratio for having a RSV-LRI with minimal breast feeding was 5.4 (95 percent CI 1.0–28.8; χ^2, $p = 0.08$). The relation between having a RSV-LRI and low maternal education had an odds ratio of 2.7 (95 percent CI 0.8–9.5; χ^2, $p = 0.2$). When both breast-feeding status and cord serum RSV antibody were considered, 100 percent (6/6) of those with lower cord serum RSV antibody, who were minimally breast-fed, had RSV-LRIs, compared with 35 percent (7/20) of those with lower cord blood RSV antibody who were breast-fed. (The OR is undefined as all cases who were minimally breast-fed had RSV-LRIs; χ^2, $p = 0.02$.) Conversely, there was no significant association between breast-feeding status and RSV-LRIs in those with higher cord serum RSV antibody (OR = 1.0; 95 percent CI 0.1–8.6; χ^2, $p = 1.0$).

DISCUSSION

A statistically significant protective effect of breast feeding against RSV-LRIs has been observed in this population. As in other studies (6, 9), it is relatively subtle and best demonstrated in those with lower socioeconomic status. The effect in its simplest bivariate mode is seen during the first few months of life only; this is demonstrated in both the larger survey sample and the case-control study. However, the independent significance of breast feeding does not with-

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stand controlling for other implicated factors (number sharing child's room, maternal education, sex); it remains statistically significant as an interaction with maternal education. Infants of mothers with a high school education or less appear to be protected against having RSV-LRIs by breast feeding in general and more so by exclusive breast feeding, but significantly only up to 3 months of age.

Others have documented the importance of the level of maternal education as a risk factor for infections (26). Although the latter study showed only marginal significance of a protective breast-feeding effect in those with 12 years of education and a nonsignificant trend in those with <12 years, the lack of any protective effect in those with ≥13 years of education is consistent with our findings.

The number of others sharing the same room with the index child, as a measure of crowding, was clearly an important risk factor for RSV-LRIs, especially when there were two or more sharing. In addition, the risk increased with a combination of lower socioeconomic status conditions plus minimal breast feeding. In other studies, various indices of crowding have been shown to be important in RSV infections (4) and in acute bronchiolitis (27, 28). The number of siblings has been shown to have an impact on infection and LRIs (10, 27–29). Although we have not considered separately the number of siblings as a risk factor, it was highly correlated with the number of persons sharing the child's room.

The case-control study shows a small protective effect against RSV-LRIs for those infants having higher cord serum RSV antibody titers, compared with those with lower levels. Those with lower cord serum RSV antibody titers, who also had minimal breast feeding, were especially at high risk for a RSV-LRI in the first few months of life. The smaller number of cases in the case-control study limits the number of risk factors that can be considered. However, it is clear that combinations of risk factors which include lower cord RSV antibody increase the likelihood of a child having a RSV-LRI. The relative risk of having a RSV-LRI increased from 1.6 for those with lower cord serum RSV antibody to 2.2 for those who also had minimal breast feeding to 4.4 for those who, in addition, had a lower maternal education. We find no evidence to support the hypothesis (12, 16) that a higher cord serum RSV antibody titer may increase susceptibility to RSV-LRIs.

In developing nations, the evidence for a protective effect of breast feeding is thought to be more conclusive (8, 30). It seems likely that any protective effect of breast feeding demonstrated in the more developed nations would be observed mainly in those segments of the community where infection would be more probable, e.g., as found in the present study, in conditions of lower socioeconomic status (measured here by maternal education and/or crowding), which may approximate those of the less developed world. Wright et al. (19) have shown in this same population a protective effect of breast feeding in relation to early wheezing LRIs, especially in crowded conditions.

It is plausible to speculate that there may be several effects of breast feeding on the lung. There may be an effect on lung development (31), possibly mediated by growth factors (32–34). Also, there may be additional immunologic benefits of breast feeding. There is also the possibility that the act of breast feeding itself limits the chances of infection by reducing the number of persons who have regular contact with a young infant.

Two potential mechanisms of protection have been demonstrated. 1) This and other studies relate infant RSV antibody levels inversely to various aspects of RSV infection, including severity and age (3, 11). 2) Human colostrum has been shown to contain neutralizing activity (partly immunoglobulin A) against RSV in vitro (5, 15). However, the method of acquiring antibody as well as its mode of action may not necessarily involve breast feeding. This study shows no additional protection associated with breast feeding against RSV-LRIs in those who already have a higher cord serum RSV antibody level, compared with a pro-

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tective effect of breast feeding in those with lower cord blood titers. The nature of this effect is speculative and may or may not involve passively acquired antibody from breast milk. Cell sizes for these analyses are, however, very small. Interestingly, some have suggested that, since infants have been shown through radiologic studies to aspirate milk during feeding, the immunoglobulin A localized in the respiratory tract might protect against severe respiratory infection (5).

Considering birth month, Carlsen et al. (27) have shown that those born during the summer months who were approximately 6 months old at the time of the RSV outbreak were most at risk for RSV bronchiolitis. Our analysis is consistent with this finding, since the highest incidence rate (per 100 children) over the entire first year was found for those born between July and September. Glezen et al. (3) have also shown a three times greater risk of RSV infection for infants born during the 6-month period ending with the peak of the epidemic. In the Children's Respiratory Study population, the relative risk of having a RSV-LRI in the first year of life if born between July and December was 1.5 times more than for those born from January to June. In addition, the cord serum RSV antibody titer was significantly lower for those born between July and December, compared with those born between January and June.

The epidemic nature of RSV as observed in other studies (35) was confirmed in this population. The simple incidence rate for RSV-LRIs in this population was 12 per 100 children in the first year of life, considerably higher than the infection rate of 3 per 100 children per year up to 2 years of age observed by Glezen et al. (35). (The incidence for parainfluenza virus type 3 LRIs in this population (data not shown) was comparable at 2.9 to the 2 per 100 children observed by Glezen et al. (35).) Advances made in laboratory techniques over the past decade and our surveillance method probably account for many of the discrepancies between the studies. In the Children's Respiratory Study, cultures for viruses have been positive in >60 percent of the LRIs cultured. This is nearly two times greater than the isolation rates reported in earlier studies (18).

Others (1, 36) have commented on the "relative sparing" of infants of ≤1 month of age from RSV bronchiolitis. This phenomenon was seen also in the Children's Respiratory Study population: no RSV-LRIs were observed up to <1 month of age and relatively few up to <3 months of age. Parrott et al. (36) found that the frequency of RSV infection did not vary widely with age between 1 and 18 months in those whose respiratory illness did not require hospitalization, with a maximum frequency of RSV infection at 2 months of age. In contrast, among those who were hospitalized, there was a distinct peak at 2 months of age. In this study, the peak incidence of RSV-LRIs is between 3 and 6 months of age. Clearly different populations have different age distributions of RSV-LRIs. It is interesting and provocative to note that the rate of breast feeding in the US population, both exclusive and supplemented with formula, has increased from 1955 to 1982 (37). Breast-feeding rates were considerably lower in the early 1970s (13.9 percent at 2 months of age in 1971) than in the 1980s (47.5 percent at 2 months in 1984) (37). The latter compares with 59 percent breast feeding at age 2 months in the Children's Respiratory Study population. This increase in breast-feeding rates could explain the later peak incidence of RSV-LRIs in the Children's Respiratory Study population in the 1980s compared with the outpatient results of Parrott et al. (36) in the 1970s.

In this population, it appears that males are more susceptible to RSV-LRIs in the early months of life; this effect was predominantly in Hispanic males. Other epidemiologic studies have shown that males are more likely than females to have RSV-LRIs up to 5 years of age (35), to be hospitalized (36), or to have more severe infections (3). Additionally, Glezen et al. (3) have observed a possible excess of infants of Hispanic origin hospitalized with RSV infections. In this study, it seems that the increased risk for RSV-LRIs associated with ethnicity was en-

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tirely due to increased RSV-LRIs in Hispanic males. This phenomenon deserves further investigation.

There may be some anatomic reasons why males have more lower respiratory tract symptomatology with RSV infections. As we have previously shown (31), low lung function predates the onset of wheezing LRIs, suggesting that infants who are born with smaller airways may be at greater risk for airway obstruction and increased respiratory symptomatology with a viral infection. We have also previously demonstrated that males are more likely to have smaller airways for their lung size than females (38). This potentially could put them at increased risk for symptomatology with viral infections. This would clearly be of more clinical importance in the first few months after birth before considerable growth has occurred.

The findings in other studies of associations between day care and increased LRIs (10, 27) are confirmed in this population for RSV-LRIs. The increase in relation to day care was observed, however, only between 7 and <9 months of age. The effect at this age also withstands controlling for other confounders. It seems plausible that the effect of day care was seen at this time because infants are more likely to be in day care after 6 months. Retrospective collection of more detailed day-care information, including age at the time of care, is currently in progress, and its analysis will be the subject of future investigations.

Regarding maternal smoking, no effect of any significance on RSV-LRIs has been demonstrated in this analysis, particularly in the early months of life. Carlsen et al. (27) also showed no effect of parental smoking in infants hospitalized with acute bronchiolitis compared with controls, although smoking rates of all parents were high. Others, however, have demonstrated a highly significant relation between parental smoking and LRIs in a community population (29), bronchiolitis in a nonhospitalized case-control study (28), and wheezing illnesses in atopic babies (39). A relation between maternal smoking, particularly ≥20 cigarettes per day, and all LRIs (wheezing or nonwheezing) has been demonstrated in our study population for the first year of life (40). We have not examined quantity of cigarettes smoked in this month-by-month analysis because of smaller numbers.

Some studies have been criticized recently for lacking methodological standards to cope with sources of bias (41–43). Since enrollees in the Children's Respiratory Study planned to use the participating health maintenance organization which serves an employed population, extreme upper and lower socioeconomic status groups may be underrepresented, as discussed previously (17). However, we have also previously concluded that the illnesses observed in the first year of life are comparable to those described in other ambulatory populations, and appropriate surveillance methods have been used (18). A priori criteria were used to establish the presence of LRI, upon which information was collected prospectively. Also, information on feeding practices was collected prospectively and, although personnel recording such information were not blinded to any LRI outcome, this was only one of many factors considered in the Children's Respiratory Study. Some retrospective information was used, but there was excellent concordance between the prospective and retrospective data. Additionally, the data collected provided information on exclusive breast feeding. Multivariate analyses have also assessed effects while controlling for other factors and their interactions.

In summary, this prospective study in a large community population has demonstrated that a variety of factors appear to increase an infant's risk for having a RSV-LRI, especially in the early months of life. These factors could be categorized into two parts: 1) likelihood of exposure to infection, including crowding and low socioeconomic status, day care, and birth month; and 2) host susceptibility to infection, including lower cord serum RSV antibody levels, being male, and being minimally breast-fed. Clearly, there are other associations between variables and categories; for example, certain birth months are associated with higher

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cord serum RSV antibody levels. Combinations of factors greatly increase the risk of having a RSV-LRI. In addition, breast feeding appears to modify the risk of having a RSV-LRI and provides protection in conditions of lower socioeconomic status where exposure may be greater.

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